Research article

Compare serum creatinine versus Renal ^{99m}Tc-DTPA scan determined glomerular filtration rates in veterans with traumatic spinal cord injury and meurogenic bladder

Meheroz H. Rabadi[1], Christopher E. Aston[2]

[1]Department of Neurology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA, [2]Department of Department of Biostatistics and Epidemiology, Oklahoma University Health Sciences Center, Oklahoma City, OK, USA

Objective: This observational study: (a) compared serum creatinine (estimated glomerular filtration rate (EGFR)) to renal isotope ^{99m}Tc-DTPA (GFR) determined glomerular filtration rate, and evaluated whether either method (b) better determined the state of renal function, and (c) predict urinary tract infection (UTI), renal and urological structural lesions or mortality in veterans with traumatic spinal cord injury (SCI) and neurogenic bladder (NGB).
Design: Observational study.
Setting: VA Medical Center affiliated with Oklahoma University.
Participants: Veterans with SCI and regularly followed in SCI clinic. Demographic and clinical data, as well as, EGFR, GFR, blood urea nitrogen (BUN) and serum creatinine levels, and presence of UTI, renal and urinary bladder lesions on renal nuclear scan, renal ultrasound, and cystoscopy studies were recorded.
Interventions: None.
Main Outcome measures: Urological lesions, UTI, and Mortality.
Results: For 161 patients with SCI and NGB the mean ± SD for EGFR was 104 ± 36 and 84 ± 32 for GFR. EGFR and GFR were positively correlated ($r = 0.34$, $P = 0.015$). GFR was significantly ($P < 0.05$) more sensitive and specific in determining renal functional state. Neither measures were significant indicator for UTI, renal or urological lesions; GFR was a significant predictor of risk of death (1.2 times increase in risk per 10 unit drop in GFR) even after adjusting for age ($P = 0.040$).
Conclusion: While GFR and EGFR are comparable measures of glomerular filtration, GFR was a more informative measure of renal functional state and risk of mortality than EGFR. Neither method predicted the presence of UTI related renal or urological lesions.

Keywords: Glomerular filtration rate, Renal isotope scan, Serum creatinine, Urinary tract infection, Observation

Introduction

Patients with traumatic spinal cord injury (SCI) and neurogenic bladder (NGB) are at an increased risk of developing renal insufficiency, and these patients need to have their renal function measured on a regular basis.[1] Renal insufficiency is due mainly to vesicoureteral reflux, recurrent urinary tract infection (UTI), hydronephrosis, and renal calculi. Preservation of renal function is one of the primary goals of a SCI program.

The Veterans Affairs (VA) directive stipulates that veterans with SCI and NGB should be tested for blood urea nitrogen (BUN) and serum creatinine levels, automated (estimated) serum creatinine determined glomerular filtration rate (EGFR) and urinary analysis on each follow-up visit to assess renal function. They should have a yearly renal ultrasound to evaluate renal structure, a radionuclide (^{99m}Tc-DTPA) renal scan to evaluate structure and function by measuring GFR, a urology consult for cystoscopy to evaluate

Correspondence to: Meheroz H. Rabadi, OUHSC, Veterans Affairs Medical Center at Oklahoma University, 921 NE 13th Street, Oklahoma City, OK 73104, USA. E-mail: rabadimh@gmail.com

DOI 10.1179/2045772315Y.0000000044

bladder structure and a urodynamic study to evaluate bladder function when needed. They should have a bladder management program in place based on specific bladder dysfunction.

The best measure of renal function is the glomerular filtration rate (GFR).[2] Normal GFR values in an adult men is 120 mL/min and in an adult women 100 mL/min. In health, GFR remains constant due to intra-renal regulatory mechanisms. In disease, GFR falls and the renal ability to regulate blood volume, maintain composition of body fluid, and eliminate waste products declines. Several exogenous and endogenous markers can be used for measuring GFR. An ideal marker is one freely filtered across the glomerular membrane that is neither absorbed nor secreted by the renal tubules.[3] Inulin, a large sugar molecule fulfills all the criteria for an ideal filtration marker and its renal clearance is considered the gold standard for GFR measurement. However, in a patient with SCI it is not practical in clinical practice as it requires precise intra-venous infusion of inulin to achieve steady-state plasma concentration and frequent timed urine collection with complete bladder emptying. Urea clearance is not used as a measure of GFR as it is not an accurate measure of GFR and as urea level is influenced by factors such as protein intake, state of hydration, presence of GI bleed and infection. Creatinine is an endogenous marker, handled by the kidneys in a similar manner to inulin, so its serum level can be used to measure GFR. Creatinine clearance (Cc) is commonly used in clinical practice to measure GFR, as creatinine production (mainly from the muscle cells) is constant and little affected by protein intake.[4] Cc can be estimated from serum creatinine using the Crockcroft and Gault (CG) equation (which corrects for age, sex, and weight, factors known to affect GFR).[5] The Cc value based on the CG equation was found to approximate in able-bodied persons; however, it overestimated the true Cc in patients with SCI.[6,7] Cc has been shown to closely correlate with insulin clearance, a gold standard in determining GFR.[6] Recently, cystatin C has been shown to be a reliable marker in detecting renal deterioration in patients with SCI.[8] It is mainly produced by nucleated cells at a steady rate and is not influenced by age, gender or muscle mass.[8] At the VA Medical Center (VAMC) renal function is measured either by serum creatinine-determined GFR or by radionuclide (DTPA technetium 99 m (^{99m}Tc-DTPA)) scan. The ^{99m}Tc-DTPA is considered the radiopharmaceutical of choice as its excretion is primarily by glomerular filtration, and has been found to be an accurate measure of GFR in adults.[9,10] In comparison to serum creatinine determined GFR measuring renal function, using. ^{99m}Tc-DTPA is time consuming, expensive and labor intensive with the need for patient to be hydrated prior to undergoing the procedure. There is also the risk of adverse-effects of a radio-nucleotide dye, and being exposed to radiation. However, serum creatinine concentration is dependent on age, age-associated decrease in renal excretion (glomerular filtration); and muscle mass, which is decreased in patients with SCI due to muscle atrophy from denervation and inactivity.[11] Serum creatinine level was not found to be a sensitive measure in detecting early deterioration of renal function in 36 patients with SCI.[1,12] Accurate measurement of 24-hour urine creatinine clearance is the practical approach to determining GFR in ambulatory patients. However, 24-hour urine collection is difficult in patients with SCI and NGB, which therefore limits the utility of the test.[13–16]

The aim of this study was to compare measures of serum creatinine-based EGFR to radionuclide-based GFR in SCI patients, determine which method was a better measure of renal functional state, and whether either method could predict increased risk of UTI related renal or urological structural lesions, or mortality in veterans with SCI and NGB. Showing EGFR as an equal or better method than GFR in measuring renal functional state would result in a reduction in patient exposure to radionuclide dye and radiation, and in a cost savings for the institution

Methods

Participants

The local Institutional Review Board for Human Subjects Research and the local Veterans Affairs Research and Development Committee approvals were obtained for the study.

On retrospective chart review there were 161 veterans with SCI registered in the SCI program at the Oklahoma City VA Medical Center (VAMC) from 1/1/2000 through 12/31/2012 (end of study period), who have been followed routinely (every 4 months for the first year and annually thereafter). All patients with SCI seen in the clinic during this time frame were included. Veterans with SCI are enrolled in the VA program within a year of their injury. Data collected from chart review included age of injury, gender, ethnicity, level and severity of injury American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade: A, B, C, D and E,[17,18] etiology (motor vehicle crash, gunshot wound, fall, diving, or other), age at onset of SCI, time since onset of the SCI, and presence of UTI (based on urine analysis showing presence of significant bacteriuria ($\geq 10^5$ cfu/ml) in the presence of nitrites and

WBC > 10/HPF, a positive urine culture, and in the presence or absence of symptoms or signs such as fever (>100° Fahrenheit), chills, lethargy, increasing muscle spasms, Autonomic Dysreflexia, malodorous and cloudy urine, lower abdominal pain/tenderness provided no other potential etiology for these non-specific complaints were identified).[19] These data were recorded in the chart on their initial evaluation and subsequent follow-up visits by a certified physician at the VAMC. Estimated serum creatinine based GFR (EGFR), renal isotope scan (^{99m}Tc-DTPA) determined GFR, blood urea nitrogen (BUN) and serum creatinine levels, renal ultrasound, cystoscopy and urodynamic study findings were also recorded on their initial evaluations and subsequent follow-up visits. Survival was recorded up to 12/31/2012.

Statistical analyses

Group descriptive statistics are expressed as mean ± standard deviation and grouped frequencies. Differences between groups were assessed using the Generalized Linear Model framework. In the simplest case of two group comparisons this was equivalent to using *t*-tests for continuous variables and χ^2 for categorical data, but allowed generalization to include covariates in the model. Covariates considered were those shown to have statistically significant association with the dependent variable in previous studies such as age at the time of injury, severity of injury (AIS grade), and duration since SCI. Area under the non-parametric receiver operant characteristics (ROC) curves (AUC) were used to determine if either GFR or EGFR provided significant prediction of the presence of renal abnormalities and to compare one method to the other. Presence or absence of renal abnormalities as determined by renal ultrasound was used as the gold standard. Correlating the ROC curve to the underlying GFR and EGFR values provided estimates of sensitivity and specificity at the 60 mL/min and 90 mL/min/1.73 m^2 cut points for each method, respectively. Data analyses were conducted using IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 20.0. IBM Corp., Armonk, NY). Results corresponding to P-values lower than 5% are described as significant and reported.

Results

The mean age of this study population ($n = 161$) was 59 ± 14, 98% were men (Table 1). The mean serum BUN was 308 ± 308 μmol/L (range 6.8–2258),

Table 1 Study population characteristics (Mean ± SD)

	All SCI patients ($n = 161$)	Motor Complete SCI ($n = 83$)	Motor Incomplete SCI ($n = 78$)	P-value, complete vs. incomplete
Age (years)	59 ± 14	60 ± 13	59 ± 15	0.41
Sex, Men:Women	157:4	83:0	74:4	0.053
Age of injury (years)	39 ± 16	37 ± 14	41 ± 17	0.12
Weight (kg)	83 ± 22	85 ± 22	82 ± 23	0.48
Height (cm)	178 ± 13	178 ± 8	152 ± 15	0.18
Body Mass Index (kg/m^2)	26.5 ± 6.6	24.3 ± 5.5	28.7 ± 7	0.003
Serum urea (μmol/L)	308 ± 308	342 ± 410	291 ± 171	0.25
Serum creatinine (μmol/L)	83 ± 77	76 ± 76	92 ± 76	0.22
GFR (mL/min)	84 ± 32	84 ± 32	84 ± 32	0.94
EGFR (charted) (mL/min)	104 ± 36	118 ± 39	86 ± 21	0.0007
EGFR (calculated) (mL/min)	104 ± 40	118 ± 46	90 ± 26	0.00001
Urological lesions n (% of 119)	56 (47%)	38 (54%)	18 (37%)	0.59
# Urinary tract infections	1.2 ± 2.5	2.1 ± 3.2	0.3 ± 0.7	0.000004
Urinary tract infection (yes) n (%)	62 (39%)	46 (55%)	16 (21%)	0.000005
Mortality n (%)	73 (45%)	50 (60%)	23 (30%)	0.00013
Cause of death				
Cancer				0.051
Cardio	11 (15%)	6 (12%)	5 (22%)	
Respiratory	13 (18%)	6 (12%)	7 (30%)	
Sepsis	17 (23%)	14 (28%)	3 (13%)	
UTI	6 (8%)	5 (10%)	1 (4%)	
Other/Unknown	9 (12%)	9 (18%)	0	
	17 (24%)	10 (20%)	7 (30%)	

SCI = Spinal Cord Injury.
Motor Complete SCI = AIS grades A & B, Motor Incomplete SCI = AIS grades C, D & E; EGFR = Creatinine determined glomerular filtration rate (mL/min/1.73m^2); (charted) EGFR value from chart ($n = 51$).
(calculated) EGFR is calculated using the Modification of Diet in Renal Disease (MDRD) Study equation and the creatinine values from the chart ($n = 157$). EGFR units are mL/min/1.73 m^2.
GFR = Glomerular filtration rate.

creatinine was 84 ± 76 μmol/L (range 7.6–557), and for EGFR and GFR was 104 ± 36 mL/min/1.73 m^2 and 84 ± 32 mL/min, respectively. At the VAMC the normal range for serum BUN and creatinine levels are 102–410 μmol/L and 46–99 mg/dl respectively. The cut scores considered abnormal for EGFR is 90 mL/min/1.73 m^2 and for GFR is 60 mL/min or less. The urological lesions found in 119 patients that had a renal ultrasound were: renal atrophy in 12 (10%), simple renal cysts in 26 (22%), renal calculi in 15 (13%) and hydronephrosis in 9 (8%) cases. In 22 patients that had a cystoscopy, urinary bladder calculi and urinary bladder thickening were found in 5 and 1 (23% and 4%) cases, respectively.

The Modification of Diet in Renal Diseases (MDRD) study[20] equation was used to calculate the GFR from the serum creatinine level (calculated GFR). This was compared it to the charted GFR (EGFR). Both had similar values (Table 1). This confirmed the accuracy of the charted EGFR values.

Figure 1 shows the positive relationship between the EGFR and GFR in patients with SCI with $r = 0.34$ (P = 0.015). Figure 2 shows the ROC curves for EGFR and GFR. The area under the ROC curve (AUC) showed GFR to be a more sensitive and specific method than EGFR for measuring renal function. For GFR the AUC = 0.96 was close to 1 and the null hypothesis of being non-informative was rejected ($P < 0.001$); for EGFR the AUC = 0.66 was lower but the null hypothesis of being non-informative was again rejected (P = 0.013). The AUC for GFR was significantly greater than for EGFR ($P < 0.05$) so GFR is significantly more informative than EGFR. With the 60 mL/min cut point for GFR the test has a sensitivity of 73% and a specificity of 95%; with a cut point of 90 mL/min/1.73 m^2 for EGFR the test has a sensitivity of 58% and specificity of 60%. This poorer sensitivity and specificity for EGFR can be seen in Figure 1 by the larger number of abnormal participants above and normal participants below the EGFR cut point compared to those to the right and left of the GFR cut point. Neither method could account for the variation in renal function for UTI related renal and urological lesions. EGFR did not vary significant (P = 0.69) with the severity of SCI injury in the whole study population but did reach significance (P = 0.0076) when only those SCI patients who were alive were considered, with higher EGFR for those with complete SCI injury (AIS

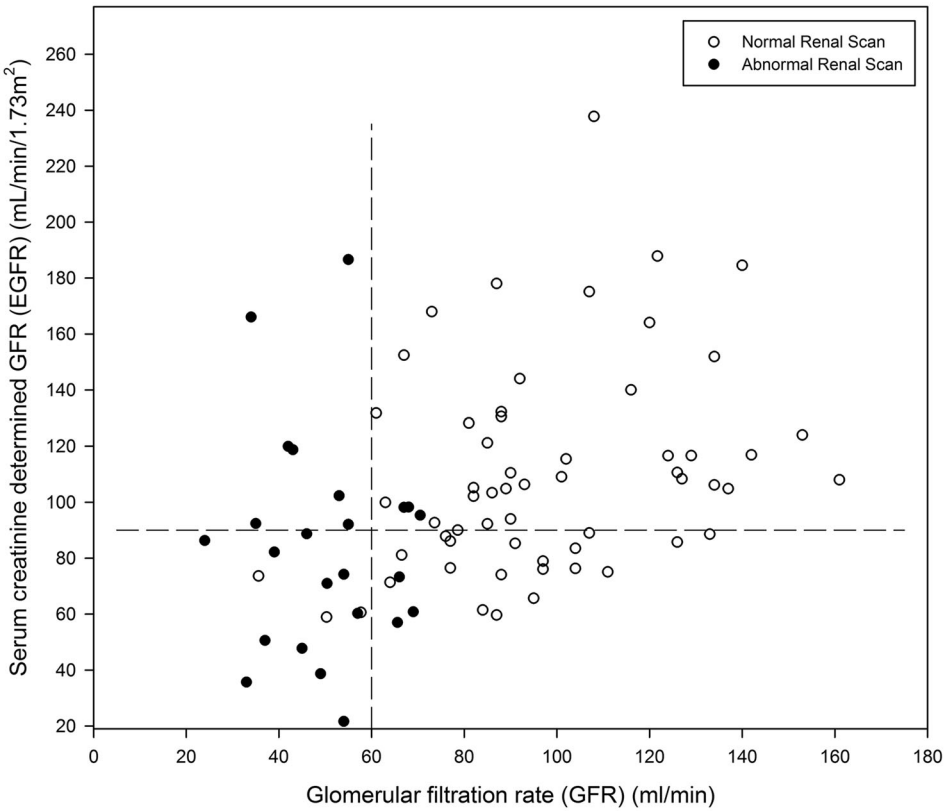

Figure 1 Glomerular Filtration Rate (GFR) and estimated GFE (EGFR) in patients with Spinal Cord Injury. Cut points for GFR and EGFR are indicated. Those to the left of the GFR = 60 cut point would be designated abnormal by GFR; those below the EGFR = 90 cut point would be designated abnormal by EGFR. Those determined to be abnormal by renal scan are shown by filled in circles (•).

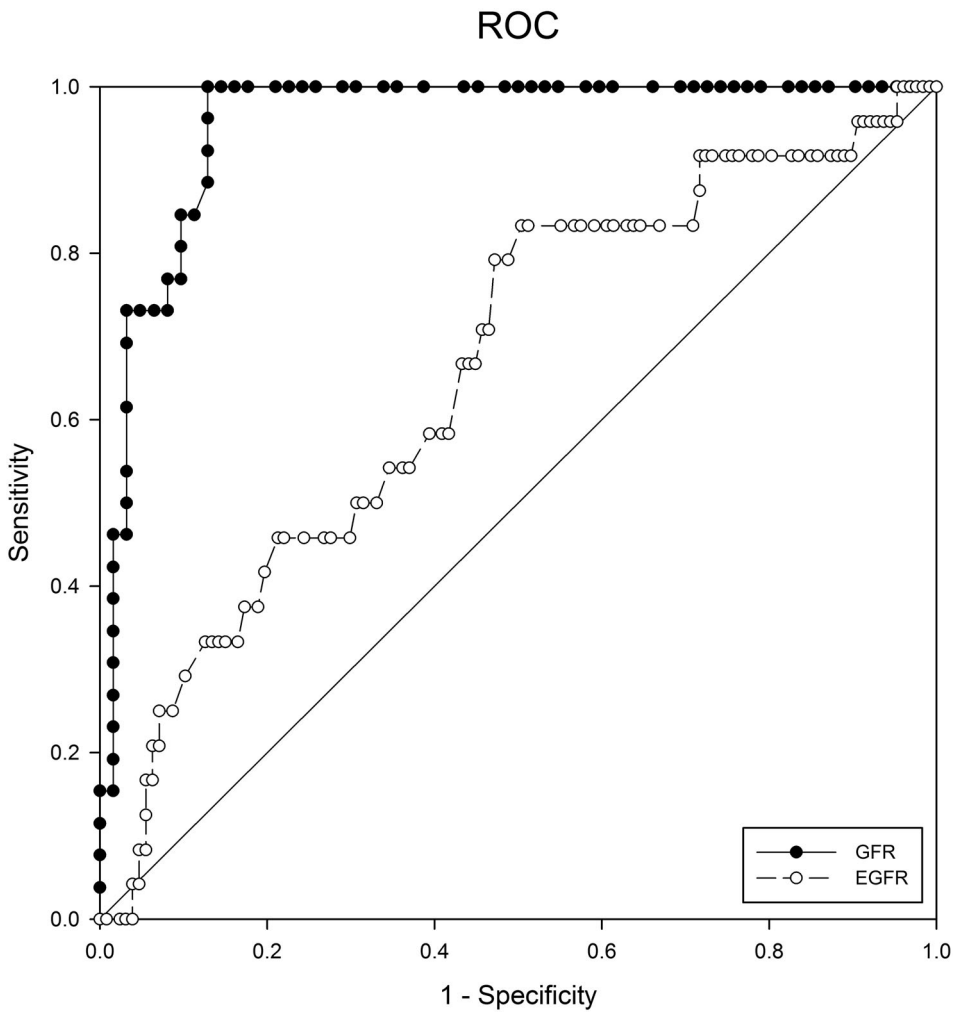

Figure 2 Receiver operant characteristics (ROC) curves for Glomerular Filtration Rate (GFR) and estimated GFR (EGFR) using presence or absence of renal abnormalities as determined by renal ultrasound as the gold standard.

A, B) 118 ± 33 ml/min compared to incomplete (AIS C, D, E) 95 ± 33 ml/min. However, only a small number of patients where available for the complete vs. the incomplete SCI group comparison (25 vs. 46). GFR did not vary significantly with the severity of SCI injury in either the whole study population (P = 0.94) or in those still alive (P = 0.69). GFR was a significant predictor of risk of death and this was maintained after adjusting for age (unadjusted P = 0.0008; adjusted P = 0.040). A 10 unit drop in GFR was associated with a 1.2 times increase in the risk of death. The causes of death were diverse with pulmonary (from COPD and pneumonia) and infection (mainly UTI) being the most common 24% and 23% respectively (Table 1). This drop in GFR could not be accounted by the causes of mortality listed in Table 1 (ANOVA, P = 0.90).

Over the 13-year follow-up period there were 51 patients with at least two GFR measurements at least a year apart. With an average time lapse of 6.4 years between measures, the rate of change in renal function by the GFR method was 1.2 units/year. There were 56 patients with at least two EGFR measurements at least a year apart. With an average time lapse of 4.7 years between measures, the rate of change in renal function by the EGFR method was −0.2 units/year.

Discussion

This is the first retrospective longitudinal study; to compare the clinical value of serum creatinine determined EGFR to radioisotope (^{99m}Tc-DTPA) determined GFR in their ability to determine renal function and structure in 161 veterans with SCI and NGB. The present study findings suggested a positive relationship between GFR and EGFR, however; ^{99m}Tc-DTPA determined GFR was a more sensitive and specific method in measuring renal function than serum creatinine determined EGFR.

The values of the (charted) EGFR were shown to be similar to values of the (calculated) EGFR determined using the Modification of Diet in Renal Diseases (MDRD) study[20] equation. Therefore, the automated serum creatinine GFR is as reliable as that calculated using the MDRD equation. Serum creatinine based EGFR is a more accurate estimate of GFR than GFR determined from a 24-hour urine collection. However, serum creatinine based EGFR is a less accurate measure of renal function for EGFR values of 60 mL/min or less.

Neither EGFR nor GFR methods were able to determine deterioration in the renal function from UTI, and renal and urological lesions, given that UTI is responsible for increased morbidity[21] by increasing the risk for autonomic dysreflexia, spasticity, and the need for frequent hospitalization resulting in decreased quality of life.[22] GFR was able to determine increased risk for mortality even when controlled for age. A 10-unit drop in GFR increased risk of death by 1.2 times. In this study the drop in the GFR values could not be accounted for by the causes of death studied. Among those dying with one of the five most common causes in this sample, deaths in veterans with low GFR (<60) was due mainly to respiratory causes followed by cardio with the caveat that the numbers are too small for these differences to be statistically significant. The rate of decline in renal function over the 13-year follow-up period was slow (by the GFR method was 1.2 units/year, and for the EGFR method it was –0.2 units/year). Neither of these rates was significantly different from zero.

After obtaining baseline EGFR and GFR on initial evaluation of SCI patients, we measured EGFR at follow up visits. Serum creatinine determined EGFR is a valuable screening test for presence of renal dysfunction in all patients with SCI on regular follow up visits. Radioisotopes scan determined GFR should be undertaken annually in those with established renal dysfunction as evidenced by a gradual decline in the EGFR values overtime, recurrent UTI, or high pressure bladder voiding.

There are several limitations of this study: First, this study was limited to a veteran population, which is predominantly comprised of white men, so it may not be generalizable to the general population. Second, the relative small sample size may have precluded detection of significant differences between groups. Third, this was a single center study. Finally, there is the possibility of inherent bias that is associated with the retrospective analysis of the data. However, there are strengths in this study lies in the completeness of the data captured by the standardized SCI registry over a 13 year period with no patient lost to follow-up and the number of patients enrolled as some of the previous studies have been quite small.[1]

Conclusion

Our study shows that (1) the radioisotope (^{99m}Tc-DTPA) determined GFR is a better determinant of renal function than EGFR; (2) neither GFR nor EGFR were significant indicators of risk for UTI, and for renal or urological structural lesions; (3) GFR predicted increased risk of mortality; and (4) the rate of decline of renal function was slow by either method. These results suggest that we should continue with the present practice of using EGFR as a renal function screen and only undertake annual radioisotope renal scan to determine renal function and structure in patients with SCI who have NGB.

Acknowledgments

CEA was funded for this study by the National Institutes of Health, National Institute of General Medical Sciences, grant 1 U54GM104938.

Disclaimer statements

Contributors Hypotheses, data collection, data formatting, wrting manuscript: MHR. Data analyses, writing manuscript: CEA.

Funding None.

Conflicts of interest None.

Ethics approval Local IRB Approval Obtained.

References

1 MacDiarmid SA, McIntyre WJ, Anthony A, Bailey RR, Turner JG, Arnold EP. Monitoring of renal function in patients with spinal cord injury. BJU Int 2000;85(9):1014–8.
2 Thomas L, Huber AR. Renal function—estimation of glomerular filtration rate. Clin Chem Lab Med 2006;44(11):1295–302.
3 Smith HW. Principles of renal physiology. New York: Oxford University Press; 1956.
4 Alleyne GA, Millward DJ, Scullard GH. Total body potassium, muscle electrolytes, and glycogen in malnourished children. J Pediatr 1970;76(1):75–81.
5 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41.
6 Mirahmadi MK, Byrne C, Barton C, Penera N, Gordon S, Vaziri ND. Prediction of creatinine clearance from serum creatinine in spinal cord injury patients. Paraplegia 1983;21(1):23–9.
7 Kuhlemeier KV, McEachran AB, Lloyd LK, Stover SL, Fine PR. Serum creatinine as an indicator of renal function after spinal cord injury. Arch Phys Med Rehabil 1984;65(11):694–7.
8 Thomassen SA, Johannesen IL, Erlandsen EJ, Abrahamsen J, Randers E. Serum cystatin C as a marker of the renal function in patients with spinal cord injury. Spinal Cord 2002;40(10):524–8.
9 Klopper JF, Hauser W, Atkins HL, Eckelman WC, Richards P. Evaluation of 99 m Tc-DTPA for the measurement of glomerular filtration rate. J Nucl Med 1972;13(1):107–10.

10 Hilson AJ, Mistry RD, Maisey MN. 99Tcm-DTPA for the measurement of glomerular filtration rate. Br J Radiol 1976; 49(585):794–6.
11 Mohler JL, Barton SD, Blouin RA, Cowen DL, Flanigan RC. The evaluation of creatinine clearance in spinal cord injury patients. J Urol 1986;136(2):366–9.
12 Elmelund M, Oturai PS, Biering-Sørensen F. 50 years follow-up on plasma creatinine levels after spinal cord injury. Spinal Cord 2014; 52(5):368–72.
13 Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992; 38(10):1933–53.
14 Narayanan S, Appleton HD. Creatinine: a review. Clin Chem 1980;26(8):1119–26.
15 Chikkalingaiah KB, Grant ND, Mangold TM, Cooke CR, Wall BM. Performance of simplified modification of diet in renal disease and Cockcroft-Gault equations in patients with chronic spinal cord injury and chronic kidney disease. Am J Med Sci 2010;339(2):108–16.
16 Sepahpanah F, Burns SP, McKnight B, Yang CC. Role of creatinine clearance as a screening test in persons with spinal cord injury. Arch Phys Med Rehabil 2006;87(4):524–8.
17 American Spinal Injury Association/International Medical Society for Paraplegia. International standards for neurological function classification of spinal cord injury. Chicago. 1996.
18 Kirshblum SC, Burns SP, Biering-Sørensen F, Donovan W, Graves DE, Jha A, *et al.* International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;34(6):535–46.
19 Goetz LL, Cardenas DD, Kennelly M, Bonne Lee BS, Linsenmeyer T, *et al.* International spinal cord injury urinary tract infection basic data set. Spinal Cord 2013;51(9): 700–4.
20 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. Ann Intern Med 1999; 130(6):461–70.
21 Cardenas DD, Hoffman JM, Kirshblum S, McKinley W. Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. Arch Phys Med Rehabil 2004; 85(11):1757–63.
22 Ku JH. The management of neurogenic bladder and quality of life in spinal cord injury. BJU Int 2006;98(4):739–45.